STATEMENT OF SUBSTANCE OF INTERVIEW

An interview was held on January 11, 2007 between Examiner Ghali and Applicants' representatives, David Osborne and Ronald Burchett. In the interview summary statement, mailed January 19, 2007, the Examiner suggested amending Claim 81 to recite active agents recited in claims 87-97 as part of the transdermal formulation, with patentability to be determined upon filing the response. Additionally, Examiner Ghali and David Osborne discussed the patentability of Claim 81 if permeation enhancers and adhesive polymers were recited in the claim.

REMARKS

Claims 81, 87, 90, and 94 have been amended. Claims 98-102 have been added.

Reconsideration of the application is respectfully requested in view of the following responsive remarks. For the Examiner's convenience and reference, Applicant's remarks are presented in the order in which the corresponding issues were raised in the Office Action.

In the Office Action of September 11, 2006 the following actions were taken:

(1) Claims 82, 87-97 were rejected under 35 U.S.C. 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention;

(2) Claims 81-86 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over U.S. Pat. No. 6,352,715 (hereinafter "'715 patent");

(3) Claims 81-86, 90, and 93-97 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over U.S. Pat. No. 6,159,986 (hereinafter "'986 patent");

(4) Claims 81 and 83-86 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Chinese Pat. No. 1,111,987 (hereinafter "'987 patent");

(5) Claim 82 was rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over '987 in view of '715;

(6) Claims 90 and 93-97 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over '715 or '987 in view of '986;

(7) Claims 87-89 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over '715, '986 or '987 each in view of U.S. Pat. No. 6,524,616 (hereinafter "'616 patent");

(8) Claims 87-90, 94-95, and 97 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over '715 or '987 each in view of the article entitled "Drug Treatment for Alzheimer's Disease" by Tiffany et al. (hereinafter "Tiffany");

(9) Claims 87-89 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over '986 in view of Tiffany;

(10) Claims 90 and 93 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over any of '715 and '987 each in view of U.S. Pat. No. 5,104,880 (hereinafter "'880 patent");

(11) Claims 90 and 91 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over '715, and '987 each in view of U.S. Pat. No. 5,877,173 (hereinafter "'713 patent");

(12) Claim 91 was rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over '986 in view of '713;

(13) Claims 90-92 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over '715 or '987 each in view of U.S. Pat. No. 5,668,117 (hereinafter "'117 patent"); and

(14) Claims 91-92 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over '986 in view of '117.

It is respectfully submitted that the presently pending claims be allowed based on the remarks below.

Claim Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 82 and 87-97 as allegedly indefinite. Specifically, for claims 87, 90, and 94, the Examiner questioned the method of the administration. Claims 87, 90, and 94 have been amended to include the type of method employed, as such, no ambiguity exists as to the method of administration. Therefore, the Applicants respectfully request that the rejection be withdrawn.

Additionally, the Examiner rejected claim 82. Specifically, the Examiner questioned the expressions "salts, analogs, derivatives and prodrugs." By the present amendment Applicants have amended the claims to remove the term "derivatives". It is respectfully submitted that the number of potential salts, analogs, and prodrugs for each recited compound are well know and sufficiently identifiable as to allow one of ordinary skill in the art to easily ascertain the full compliment of possible compounds encompassed by the presently amended claims.

Rejections Under 35 U.S.C. § 103

The Examiner has rejected claims 81-97 under 35 U.S.C. 103(a) as being allegedly unpatentable over several references.

The Applicant does not deem it necessary to recite the entire case law standard required in order to establish a *prima facie* case of obviousness. However, the Applicant would like to briefly remind the Examiner of the required three criteria for a *prima facie* case of obviousness, namely that the asserted references as modified or combined must: 1) teach or suggest each and every element of the claimed invention; 2) provide sufficient motivation for the modification or combination asserted; and 3) provide a sufficient likelihood of successfully making the modification or combination.

As the Examiner has used three primary references, '715, '986, and '987, in rejecting the present claim set, a brief description of these references is provided.

The '715 Patent

The '715 patent discloses a transdermal drug system whereby Huperzine A is administered for the treatment of Alzheimer's Disease. See Abstract. The transdermal systems disclosed includes both reservoir type devices and adhesive matrix devices. See col. 2, lines 56-col. 3, line 21. While a number of traditional transdermal device components are seemingly contemplated, nothing expressly teaches the use of penetration enhancers as an individual effective means of enhancing Huperzine administration. Rather, the problematic issue in this patent is to attain a pH in the transdermal delivery device that provides enhanced penetration of Huperzine into the skin. See col.2, lines 65-col. 3, line 1. Such a pH range for Huperzine is taught to be between 7 and 9. See col. 3, 5-6; col. 3, lines 20-21; Figs. 4 and 5; Table 1 at col. 7-8; col. 8, lines 39-44; Claims 1, 5, 6, 10, 11, and 15. The improved skin penetration is taught to be the result of converting Huperzine A from its ionized form at acidic pH, to its lipophilic form at a more neutral pH, which increases its skin partitioning coefficient. See col.8, lines 24-37. The reference further teaches that only the neutral species of Huperzine A is permeable to the skin. See col. 8, lines 36-37.

Further, this reference provides both an endorsement and a caution with respect to the use of co-solvents to improve the delivery of Huperzine A. Co-solvents are seemingly suggested as possibly improving the penetration of the neutral form of Huperzine, at col. 8, lines 65-68. However, the patent also teaches that not all co-solvents may be used to effectively enhance skin permeation. Specifically, col. 8, lines 47-52, teaches that careful evaluation of co-solvents, especially non-polar solvents, such as alcohols and glycols must be made before use; as such solvents may actually reduce the partitioning coefficient of Huperzine A, and thereby reduce its penetration into the skin.

The '986 Patent

The '986 patent discloses the use of an herbal supplement for the improvement of memory. Specifically, acetylcholine boosters, such as Huperzine A are used. See col. 1, lines 34-39. More specifically, this patent discloses the coadministration of Huperzine A with a second component extracted from a suitable plant, such as an extract of hypercum perforatum (i.e. St. John's Wort) in order to attain improved efficacy. See col. 1, lines 39-43; col. 2, lines 15-27. While the herbal supplement is to be primarily formulated for oral delivery, other forms of administration, including transdermal delivery are briefly mentioned. See col. 2, lines 54-63.

The '987 Patent

This abstract of this Chinese patent as cited by the Examiner teaches a plaster for treating senile dementia containing Huperzine and laurocapram (Azone) or a mixture of laurocapram and another agent as a permeation enhancer.

Applicants contend that the Examiner has failed to meet establish a *prima facie* case of obviousness. Specifically, the Office has failed to show each and every element of the present invention in the asserted references, or combination of references. Further, the Examiner has failed to show sufficient motivation for any of the asserted references to be modified or combined as stated. Finally, Applicants contend that there is an insufficient likelihood of successfully attaining a functional product using the asserted combination of references in view of the teachings of each

reference as a whole. Since the Applicants have amended the pending claim set, each independent claim is discussed in view of the above primary references.

Claim 81

As recited in amended Claim 81, Applicants' invention resides in the improvement of a subject's memory and cognitive function by providing the subject with a huperzine blood plasma level of from about 0.1 to about 30 ng/ml. The mechanism by which such blood levels are obtains is through administration of a transdermal matrix patch which includes a combination of one or more specific adhesives and one or more specific permeation enhancers. The adhesives recited are acrylate polymer or rubber-based pressure sensitive adhesives, including homopolymers, copolymers, terpolymers, thereof. The enhancers are selected from the group consisting of: fatty acids, fatty acid esters, fatty alcohols, fatty acid esters of lactic acid, fatty acid esters of glycolic acid, amides, amines, pyrrolidones, glycerol trimesters, terpenes, their salts, and mixtures thereof, and specifically exclude Azone.

None of the references, either alone, or in combination teach or suggest either that the attainment of such serum levels would provide improved memory and/or cognitive function, or that such serum levels could be attained and sustained using the specifically recited formulations. The '715 patent does not teach the use of pressure sensitive adhesives with permeation enhancers. The solvents used to dissolve Huperzine A in the pressure sensitive adhesive "are removed" to form the transdermal delivery system. See col. 9, lines 50-51. As such, the transdermal delivery system is free from any substance that could be considered a permeation enhancer. Additionally, the '715 patent does not teach the recited Huperzine blood plasma levels.

Moreover, the '715 reference effectively teaches away from using a penetration enhancer at all in view of its teachings of adjusting pH in order to enhance penetration, and is even further distant from the use of a penetration enhancer in a matrix patch. As the Applicant has raised the issue of teaching away, the Applicant would like to review the current case law regarding teaching away for the Examiner's convenience. The Court of Appeals for the Federal Circuit has clearly stated that "an applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away

from the claimed invention in any material respect." In re Petersen, 315 F.3d 1325, 1331 (Fed. Cir. 2003). The Court has also stated that "[w]e have noted elsewhere, as a 'useful general rule,' that references that teach away cannot serve to create a prima facie case of obviousness." (emphasis added) McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1354 (Fed. Cir. 2001). In identifying the appropriate standard for teaching away, the Court has further stated:

> "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be **discouraged from following the path set out in the reference**, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, **a reference will teach away if it suggests** that the **line of development** flowing from the reference's disclosure **is unlikely to be productive** of the result sought by the applicant." (emphasis added) In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

The '715 patent clearly would discourage one of ordinary skill in the art from using permeation enhancers, because the primary mechanism of penetration enhancement is taught to be the adjustment of the pH. While there is a small mention of the use of "cosolvents" to further aid the pH factor with penetration, it is Applicant's position that such "cosolvents" are not penetration enhancers per se as they would not survive the drying process for a matrix patch and remain in the final formulation. Moreover, assuming *arguendo* that such compounds would in fact survive the drying process and make it into a final matrix patch, the '715 states some solvents actually "reduce partitioning of drugs to the skin," and provides no guidance whatsoever on what solvents might further help penetration as opposed to those that might actually reduce penetration. Such a teaching is in direct conflict with the general definition of permeation enhancer, and one of ordinary skill in the art would certainly not be led to the use of the specific penetration enhancer group recited in the currently amended claim.

As such, '715 reference cannot be used to create a prima facie case of obviousness since it effectively teaches away from the use permeation enhancers. Therefore, the Applicants respectfully request that the Examiner withdraw the present rejection.

The '986 patent also does not teach or suggest each and every element of amended Claim 81.

While the reference broadly mentions transdermal formulations, nothing teaches or suggests an adhesive matrix patch. Also, nothing teaches or suggests the use of specific adhesives for the matrix. Furthermore, nothing teaches or suggests the use of permeation enhancers, and nothing suggests those enhancer compounds now recited in the presently pending claims. As such, the '986 reference is completely lacking in anything that would lead one of ordinary skill in the art to arrive at the specific transdermal matrix patch formulations now claimed.

The '987 patent also does not teach or suggest each and every element of amended Claim 81. Nor would its teachings lead one of ordinary skill in the art to the combination of specific ingredient required thereby. The '987 patent requires the use of Azone in order to delivery Huperzine transdermally. Claim 81 as presently amended expressly excludes Azone and requires one of a select list of other permeation enhancer agents. The specification of the present application even specifically states:

> One enhancer that has been found to be unacceptable is Azone. Although Azone may provide penetration enhancement of various substances, the side effects experienced are considered intolerable. Particularly, Azone has been deemed unusable because of the severe skin irritation that results. Not only does Azone cause irritation to all layers of the epidermis, but also irritates all the dermis layers as well. Further, the skin irritation caused by Azone is irreversible damage, which results in alteration of the tissue and scarring. See page 23, line 20 through page 24, line 6.

Since the '987 patent requires the use of Azone to achieve its therapeutic levels and the present claim explicitly excludes the use of Azone, the '987 patent fails to teach or fairly suggest each and every element of presently amended claim 81. Therefore, based on this strong and central requirement for the use of Azone, one of ordinary skill in the art would not be lead to consider other penetration enhancers, and would certainly not be led to the list presently required by Claim 81r withdraw the rejection.

As such, nothing in any of the references asserted by the Examiner either separately, or in combination fairly teaches or suggests each and every element of amended Claim 81.

Accordingly, the Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness, and Applicants respectfully request that the rejection be withdrawn.

In addition to the rejections of the independent Claim 81, the Examiner also rejected the various dependent claims in view of the combination of the foregoing reference in view of some additional references. Applicant's respectfully submit that as the dependent claims depend from the independent claim, that such claims are also patentably distinct from the prior art in view of the fact that Claim 81 is patentably distinct.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that presently amended Claims 81-102 are patentably distinct from the asserted prior art references and are allowable, and prompt allowance thereof is respectfully requested.

If any impediment remains to prompt allowance of the claims after consideration of the above-recited amendments and remarks, which could be alleviated during a telephone interview, the Examiner is invited to telephone the undersigned attorney at (801) 566-6633 so that such issues may be resolved as expeditiously as possible.

Please charge any additional fees except for Issue Fee or credit any overpayment to Deposit Account No. 20-0100.

Dated this 12th day of February, 2007.

Respectfully submitted,

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